REMARKS/ARGUMENTS

Claims 1-11 are pending in this application. According to the Office Action mailed March 25, 2004, these claims are finally rejected. Claim 1 has been amended to further distinguish the invention from the prior art. The amendments to claim 1 are supported by the application as filed and thus they do not introduce any new matter. In particular, support for the amendments to claim 1 may be found, *inter alia*, in Examples 1-3 on page 4 of the application wherein the micro-capsules of the invention are made with the use of dichloromethane (an organic solvent). Thus it is apparent that the peptide included in the microcapsules of the invention can not be sensible (i.e., sensitive) to or degradable by organic solvents. If they were, the microcapsules of the invention would not be capable of delivering the peptide since the solvent would have damaged or destroyed the peptide during or subsequent to the formation of the micro-capsules.. Further support for the amendments to claim 1 is found, e.g., on page 1, lines 28-35. In the paragraph at lines 28-31, applicants state that their invention allows a very effective "modulation of the liberation characteristics" of the micro-capsules, without the need to modify the composition of the polymer. In the following paragraph (at lines 33-35), applicants define "modulating release from microcapsules" as meaning, "a reduction in the initial release of encapsulated drug and a release of said drug that is almost linear in time." (Emphasis supplied). In addition to the amendment of claim 1, claims 5 and 7 have been amended to correct obvious typographical errors in these claims. Furthermore, claim 2 is amended to ensure a proper anteceedent basis for the terms therein, which amendment was occasioned due to the amendment to claim 1. These additional amendments raise no issue of new matter.

Entry of this Amendment is respectfully requested since it is believed to place all of the claims of the application in condition for allowance, or at a minimum, to materially reduce the issues for an appeal.

Rejection Under §102

Claims 1-3 are rejected under 35 U.S.C. §102(b) as allegedly anticipated by BIOGRAM AM (WO 97/14408) (hereinafter "Biogram"). This rejection is respectfully traversed for the reasons which follow.

It is well known by those of ordinary skill in this art that the physical structure of a microparticle will significantly affect the delivery profile of the drug (e.g., a peptide) included in its formulation, i.e., depending upon the physical situation of the drug within the microcapsule. For example:

(A) if the drug is located on the surface of the microcapsule an almost instantaneous liberation of the drug will take place, as the drug will begin to be delivered as soon as the microcapsule's surface starts to become degraded;

(B) if the drug is located at the center of the microcapsule, only a minimal amount of the drug will be liberated at first since the microcapsule must be degraded down to its center before the drug can start to be liberated; and

(C) homogeneous distribution of the drug throughout the microcapsule produces an intermediate effect, i.e., between (A) and (B) above.

The Biogram reference discloses a microcapsule containing a starch nucleus having a drug dispersed within the nucleus, giving rise to a delivery profile as in (B) above. In contrast, the microcapsules of the present invention are comprised of the pure drug coated by a homogeneous mixture of the polymer (i.e., the PLGA) and the citric acid ester. As the microcapsules of the present invention lack the starch nucleus described in Biogram, their delivery profiles are markedly different from those of the Biogram reference. That is, with the microcapsules of Biogram, drug delivery only begins after the microcapsule is degraded down to its center, whereupon the nucleus is breached to release the drug. In contrast, however, the microcapsules of the present invention, due to the unanticipated and previously unknown effect of the citric acid ester upon drug delivery, provide a substantially linear release profile of the peptide contained therein over time. This feature is now specifically recited in claim 1 as amended and it clearly differentiates the present invention over Biogram.

An additional feature which even further distinguishes the presently claimed invention from the disclosure of the Biogram reference is that the present invention, as now recited in (amended) claim 1, incorporates peptides which are neither sensible to (i.e., sensitive to) or degradable by organic solvents. In contrast, the Biogram reference teaches (see, e.g., p. 11, lines 24-28) that the invention described therein is <u>especially interesting</u> in connection with proteins, peptides and

polypeptides or other drugs or biologically active substances which are sensitive to or instable in the presence of organic solvents. (Emphasis supplied by applicants). Moreover, on page 7 the Biogram reference teaches to: (1)entrap the active ingredient in microparticles without using any organic solvent (lines 3-5);(2) removing very rapidly any organic solvent used for the polymer coating to avoid any substantial exposure of the active substance to organic solvent (lines 8-10); (3) preparing sustained release microparticles of a biologically active substance, especially a substance that is instable in the presence of an organic solvent (lines 12-16); and (4) creating a shell of the polymer on the core particles [i.e., the starch nucleus containing the drug] without any detrimental exposure of the active substance to the organic solvent. Biogram, provides a teaching away from incorporating within the micro-capsule a peptide which is neither sensible to or degraded by organic solvents, as now recited in applicants' claim 1, by instead teaching one of ordinary skill to eliminate such organic solvents during the formulation of the micro-particles so that the formulation may include biologically active substances that are instable in the presence of such solvents. Thus the present invention is further distinguishable from Biogram on this basis as well.

Applicants therefore respectfully submit that Biogram does not disclose each and every element of the invention as presently recited in their claim 1, as amended. Thus the Examiner is respectfully requested to reconsider and withdraw the rejection of claim 1 under §102(b) over Biogram. Moreover, as claims 2-3 both depend, directly or indirectly, from claim 1 and thus incorporate all of the recitations of the subject claim, they are also distinguishable over Biogram for the same reasons as claim 1. Thus applicants respectfully solicit withdrawal of the §102 rejection of claims 2 and 3 as well.

Rejection Under §103

Claims 4 and 5 are rejected under 35 U.S.C. §103 as being allegedly obvious to one of ordinary skill in this art over the Biogram reference. Claims 4 and 5, however, depend upon claim 1 which, for the reasons above, is distinguishable over Biogram. As there is no teaching or disclosure in Biogram suggesting to one of ordinary skill in this art to either (1) incorporate a peptide which is neither sensible to nor degradable by organic solvents; or (2) provide a micro-capsule which has a substantially linear release profile of a peptide over time, applicants submit that claims 4 and 5 are

not obvious over Biogram. Thus, the Examiner is respectfully requested to reconsider and withdraw the rejection of claims 4-5 under §103.

Claims 6-11 are rejected under 35 U.S.C. §103 as allegedly unpatentable over Biogram in view of U.S. Patents 4,954,298 to Yamamoto et al ("Yamamoto"), 5,538,739 to Bodmer et al. ("Bodmer") and 5,536,508 to Canal et al. ("Canal"). As in the case of claims 4-5 discussed above, claims 6-11 all depend, directly or indirectly on claim 1, and thus these claims incorporate all of the recitations of the subject claim. Neither Yamamoto, Bodmer nor Canal contains any disclosure which would supply, or even suggest, the aspects of the present invention missing from the Biogram reference. Thus, they do not remedy the deficiencies of Biogram in that they neither teach one of ordinary skill to (1) incorporate a peptide which is neither sensible to nor degradable by organic solvents, nor (2) to provide a microcapsule which has a substantially linear release profile of a peptide over time. Applicants submit, therefore, that their invention as presently claimed is neither anticipated by nor obvious over any of the Biogram,Yamamoto, Bodmer and/or Canal references, whether these references are taken alone or in any combination. For the reasons above, therefore, the Examiner is respectfully requested to reconsider and withdraw the rejection of claims 6-11 under 35 U.S.C. §103.

In light of the foregoing, it is respectfully submitted that this application is now in condition to be allowed and early issuance of a Notice of Allowance is respectfully solicited. If there are any issues or amendments the Examiner wishes to discuss, the Examiner is encouraged to contact the undersigned.

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as First Class Mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on July 6, 2004:

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Signature

July 6, 2004
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Respectfully submitted,

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